Strudel Inherited Cancer Syndromes Review

By Mike

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Colon- Syndromes with Polyposis (1)

Familial Adenomatous Polyposis (FAP)

- Adenomatous polyps (100s)
  - Always involves rectum
- Tx: colonoscopy age 10-12 q1y, proph proctocolectomy
  - osteoma, dental, fibromatosis? Gardner syndrome
  - metastatic brain cx-(medulloblastoma, glioblastoma)? Turcot syndrome
- Autosomal dominant, APC gene on 5q

By Department of Pathology, Calicut Medical College - Calicut Medical College, CC BY-SA 4.0,

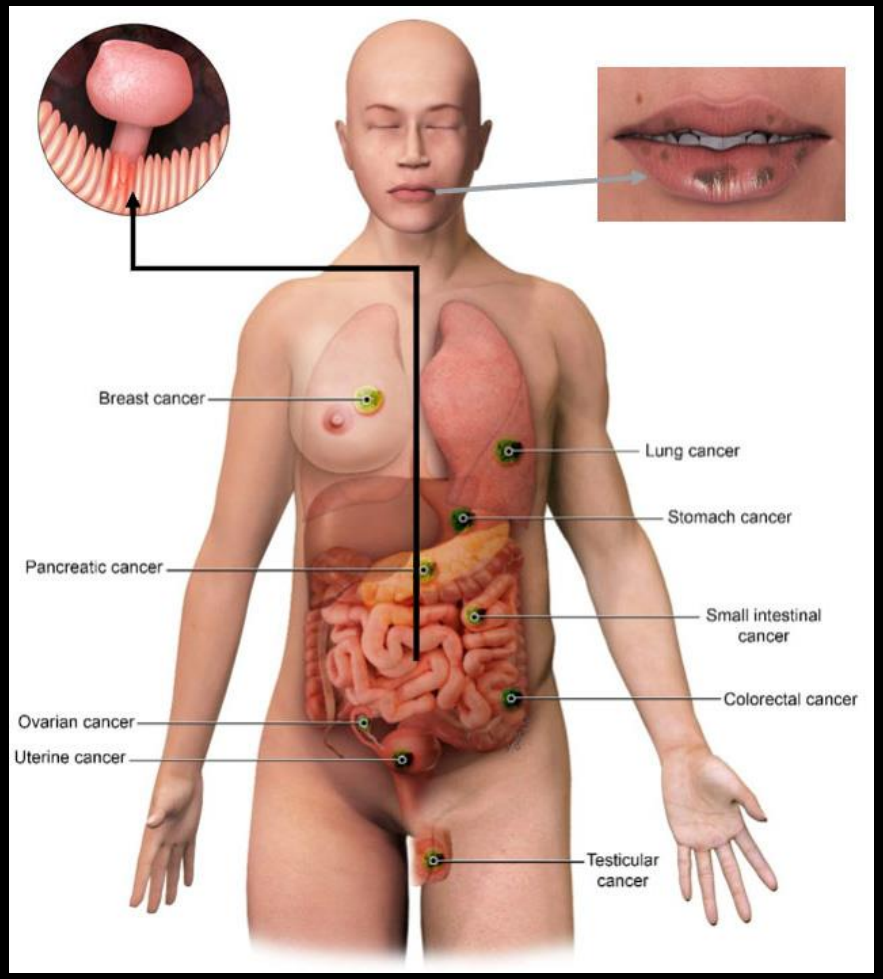
Colon- Syndromes with Polyposis (2)

Peutz-Jeghers

- Hamartomas in GI tract with PIGMENTED MACULES around lips, oral mucosa, face, palms
- Increased risk of CRC, pancreatic, stomach, breast cx
- Bleeding-may present with anemia
- STK11 gene, Autosomal dominant
  - Contrast with Osler-Weber-Rendau syndrome (Hereditary hemorrhagic telangiectasia)
    - Blanchable papules on lips
    - Thin-walled blood vessels-AVM, nosebleeds, GI bleed

- Familial juvenile polyposis coli
  - Childhood, hamartomas
  - NO pigmented macules

Peutz-Jeghers



By Klimkowski S, Ibrahim M, Ibarra Rovira JJ, Elshikh M, Javadi S, Klekers AR - Klimkowski S, Ibrahim M, Ibarra Rovira JJ, Elshikh M, Javadi S, Klekers AR (2021). "Peutz-Jeghers Syndrome and the Role of Imaging: Pathophysiology, Diagnosis, and Associated Cancers.". Cancers (Basel) 13 (20). DOI:10.3390/cancers13205121. PMID 34680270. PMC: 8533703., CC BY 4.0, https://commons.wikimedia.org/w/index.php?curid=124779180

Colon…Nonpolyposis

Lynch Syndrome

- Early onset CRC w/out polyposis
- Microsatellite instability
- CEO: colon, endometrial, epi ovarian cx
- Tx: routine scope, prophylactic colectomy not recommended
- Autosomal dominant, DNA mismatch repair genes MSH2 MLH1

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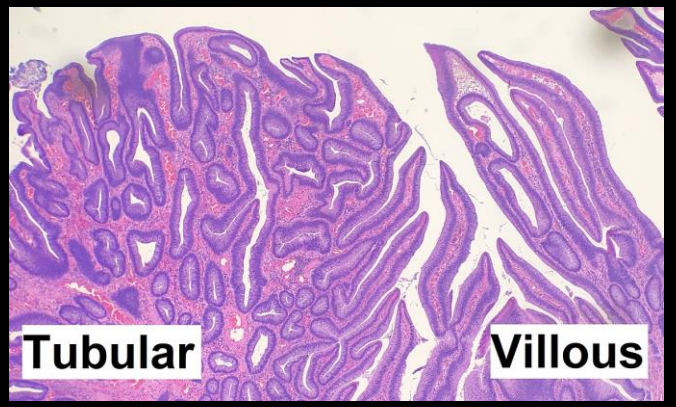
General colon cx risks

- Age
- Adenomatous polyps: villous>tubular
- Fam hx CRC
- IBD UC>Crohns
  - Start screen 8 yr following dx for UC
- Diet: high fat, low fiber
- Labs: Anemia, CEA tx response/reoccurrence, FOBT
- Dx: scope
- Tx: Resection, scope 1 yr q3yr, CEA levels



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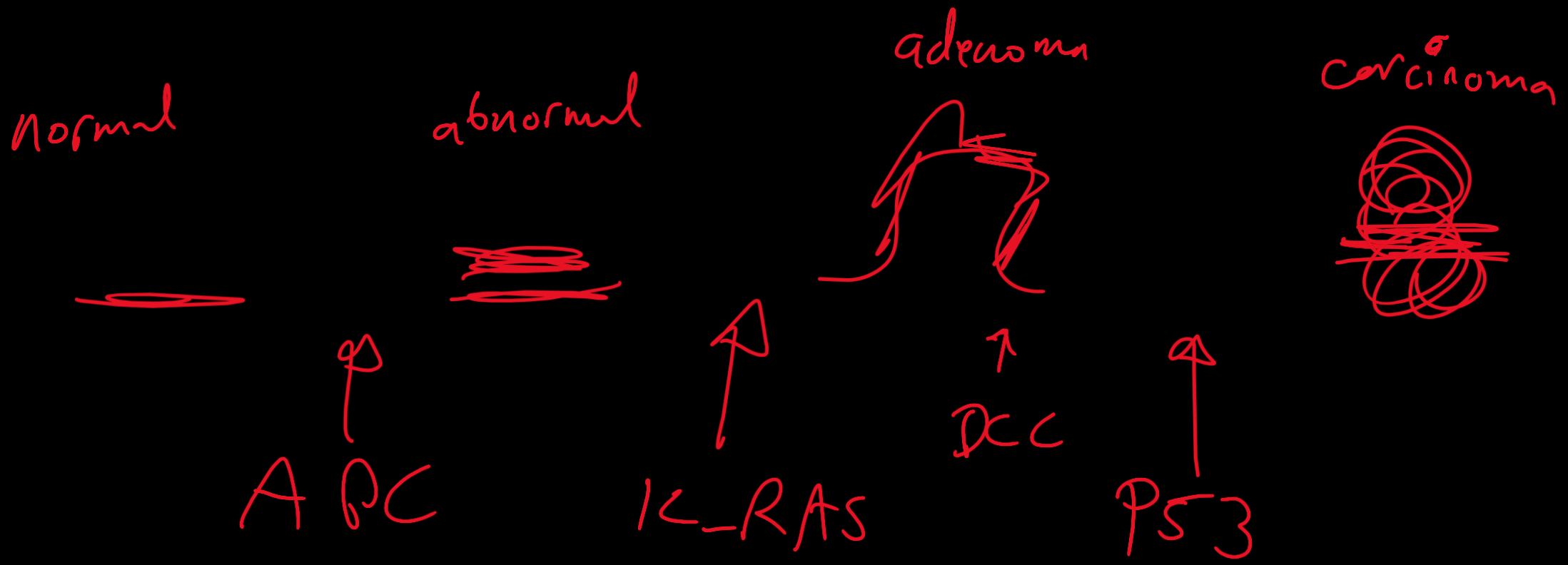
Adenoma Carcinoma Sequence

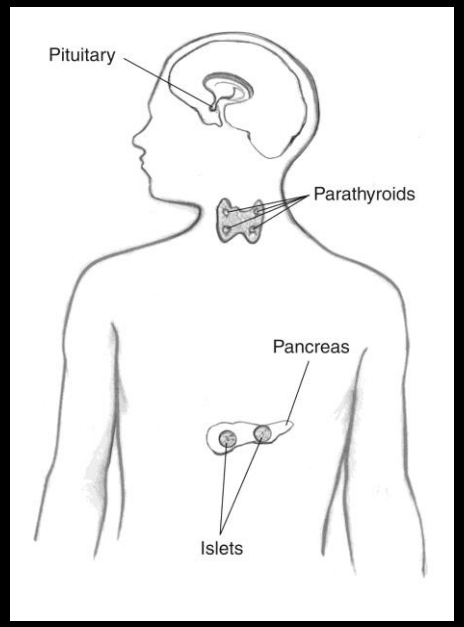
AK-53



Endocrine

Multiple Endocrine Neoplasia 1 (MEN 1)

- 3 Ps: Parathyroid, Pituitary, Pancreatic
- Parathyroid: adenoma, hyperplasia- hypercalcemia
- Pituitary: Prolactinoma, bitemp hemianopsia
- Pancreatic: gastrinoma (ZES), VIPoma (WDHA)
- MEN1 Gene mutation, aut dominant



National Institute of Diabetes and Digestive Kidney Diseases

MEN 2

- Have increased risk medullary thyroid cx **AND** pheochromocytoma
- RET gene mutation, aut dom

MEN 2A

Medullary thyroid cx, Pheochromocytoma, parathyroid hyperplasia

MEN2B

- Medullary thyroid cx, pheo, mucosal neuroma, marfanoid habitus

From Airplane! (1980)

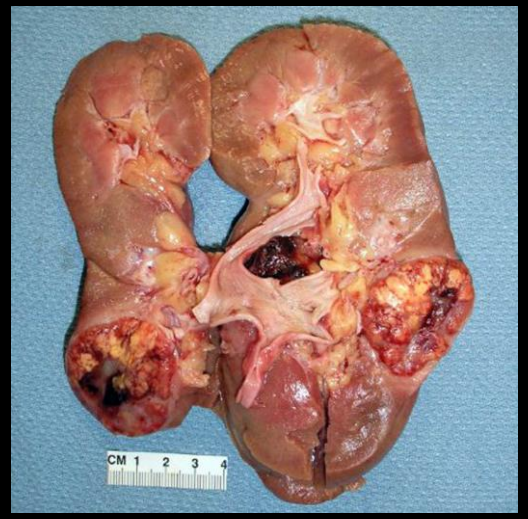
Chvostek sign
NEJM

Renal

Von Hippel-Lindau (VHL)

- Excessive angiogenesis
- HARP: Hemangioblastoma (cerebellum and retina), Angiomatosis, bl RCC, Pheo
- VHL gene on chromosome 3p
  - Uninhibited HIF1-alpha
  - Autosomal dominant

Case courtesy of Kosuke Kato, Radiopaedia.org, rID: 85490

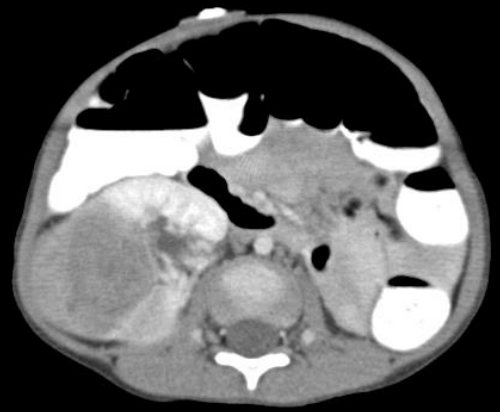


Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 9888

Wilms Tumor

- Early childhood (age 2-4)
- From glomerular cells
- WT1 and WT2 genes on chrom 11

- WAGR: Wilms, Aniridia, GU malformation, Intellectual disability (WT1)
- Denny Drash: Dysgenesis of gonads
- Beckwith-Wiedemann: Wilms, macroglossia, organomegaly, hemihypertrophy (WT2)

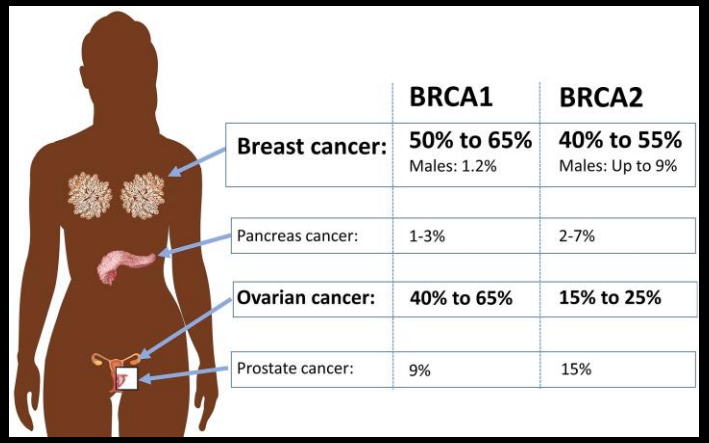


Case courtesy of Jose Rodriguez Vazquez, Radiopaedia.org, rID: 158221

Breast

BRCA1/2

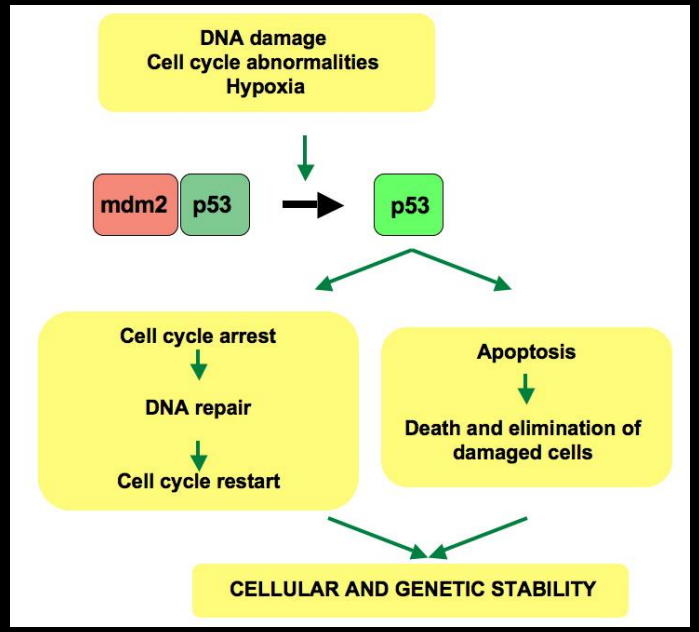
- Breast, epi Ovarian, Pancreatic
- Autosomal dominant
- dsDNA breaks-homologous recombination
- Tx: genetic counseling, consider proph mastectomy, bl salpingo-oophorectomy after childbirth
- Annual screen with TVUS and CA125



By Mikael Häggström, M.D. Author info- Reusing images- Conflicts of interest:NoneMikael Häggström, M.D. - Own workReference: Nancie Petrucelli, MS, Mary B Daly, MD, PhD, and Tuya Pal, MD.. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews, at National Center for Biotechnology Information. Initial Posting: September 4, 1998; Last Update: December 15, 2016., CC0, https://commons.wikimedia.org/w/index.php?curid=109066831

Li-Fraumeni

- SBLA: Sarcoma, Breast cx, Leukemia, Adrenal gland tumor
- Loss of p53
  - Lack G1-S cell cycle regulation
- Autosomal dominant



Thierry Soussi, Public domain, via Wikimedia Commons

Neuro

Neurofibromatosis Type 1 (NF1)

- Cutaneous neurofibromas, gliomas/meningioma, café au lait, Lisch nodules, scoliosis
- Pheochromocytoma
- Mutation in NF1 suppressor gene
  - Chromosome 17, Autosomal dominant

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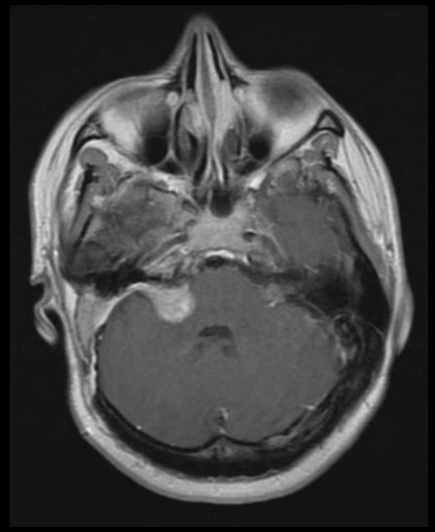
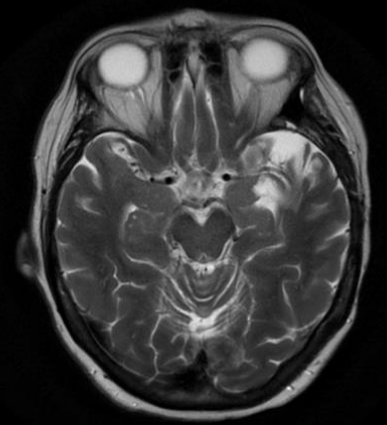
American Academy of Ophthalmology

Neurofibromatosis Type 2 (NF2)

- Presents with bilateral schwannomas, cataracts, multiple meningiomas, ependymoma.
  - Café au lait spots, neurofibroma less common
  - Schwannoma at cerebellopontine angle (VI and VIII)-hearing loss-get MRI
- Mutation in NF2 suppressor gene
  - Chromosome 22, autosomal dominant



Acoustic schwannoma of cerebellopontine angle
Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 2575



https://radiopaedia.org/cases/neurofibromatosis-type-2-with-multiple-meningiomas-1?lang=us

Case courtesy of Bruno Di Muzio, Radiopaedia.org, rID: 38271

Neuro 2

Retinoblastoma

- Presents with **white reflex (leukocoria)** in infants
  - Part of standard newborn exam
  - Sporadic vs hereditary
- Increased risk for osteosarcoma
- Mutation in Rb1 gene
  - Normally inhibits E2F to block G1 to S

American Association for Pediatric Ophthalmology and Strabismus

Tuberous Sclerosis

- Hamartomas everywhere
- Initially presents with seizures
  - subependymal nodules (hamartomas of ventricles)
- Angiofibroma, Ash leaf spot, Cardiac Rhabdomyoma, Renal Angiomyolipoma, Shagreen patches
- TSC1 or TSC2 mutation (hamartin, tuberin)
  - Autosomal dominant
  - Often variable expression

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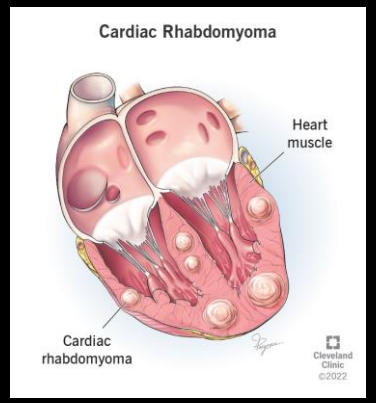
DermNet



Cleveland Clinc

Skin

Xeroderma Pigmentosum (XP)

- Sunlight sensitivity, freckled skin, corneal ulcers
- Nucleotide Excision Repair deficit
  - Unable to repair pyrimidine dimers
  - UV exposure
- Autosomal recessive

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Xeroderma Pigmentosum Society

Review Slide

System	Syndrome	Gene/Defect	Presentation	Mnemonic
Colon	FAP Peutz Jeghers Lynch	APC STK11 MSH2, MLH1	Polyposis Hamartomas CRC w/out polyposis	F(APC) none CEO
Endocrine	MEN1 MEN2A MEN2B	MEN1 MEN2A MEN2B	Parathyroid, pituitary, pancreas Medullary thyroid, pheo, parathyroid Medullary thyroid, pheo, neuroma, marfanoid	PPP Think pheo (MEN1 vs MEN2), MEN2B=marfanoid
Renal	VHL Wilms	VHL WT1, WT2	Angiogenesis everywhere (hemangioblastoma, angiomatosis, RCC, pheo) Early childhood kidney tumor (hematuria)	HARP WAGR
Breast	BRCA Li-Fraumeni	BRCA1/2 p53	Breast, Ovarian, Pancreatic cx Sarcoma, Breast, Leukemia, Adrenal	think female repro organs SBLA
Neuro	NF1 NF2 Retinoblastoma Tuberous Sclerosis	NF1 NF2 Rb TSC1, TSC2	Neurofibroma, café au lait, Lisch, scholiosis Schwannoma, meningiomas Retinoblastoma in infancy Many hamartomas, many derm findings	NF1: Backwards F to make 17 NF2: chromosome 22 Remember newborn PE Think about skin and hamartoma formation
Skin	Xeroderma Pigmentosum	NER	Excessive sunburning, increase risk skin cx	none